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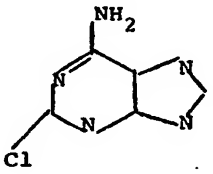
(71) Applicant
Bristol-Myers Company
345 Park Avenue
New York 10022
United States of America
(72) Inventors
Taka-aki Okita
Susumu Nakagawa
Takayuki Naito
Haruhiro Yamashita
Tetsuro Yamasaki
(74) Agents
Boult Wade and Tennant
27 Furnival Street
London EC4A 1PQ

(54) Novel purine derivatives

(57) Purine derivatives of the formula:



and wherein R is

and their pharmaceutically acceptable acid addition salts are non-adrenergic bronchodilators.

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Certain of the chemical formulæ appearing in the printed specification were submitted after the date of filing, the formulæ originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

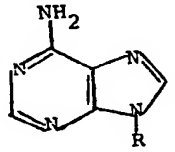
N v l purin d rivatives

This invention relates to novel purine intermediates useful as non-adrenergic bronchodilators.

Theophylline, normally administered as the ethylene-diamine salt (aminophylline) or choline salt, is a potent and useful non-adrenergic bronchodilator commonly prescribed for the treatment of brochial asthma. Because it is readily soluble, aminophylline has for many years been accepted as an effective bronchodilator when given orally. Aminophylline, however, is known to have certain disadvantages, e.g. gastric irritation and cardiovascular and central nervous system side effects, which warrant a search for new non-adrenergic bronchodilators which may have more advantageous properties such as increased potency and/or reduced side effects.

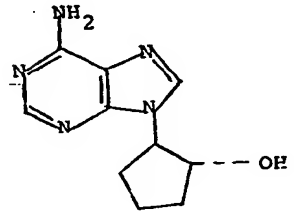
With respect to the novel compounds of the present invention, a cast number of purine derivatives have been disclosed in the patent and scientific literature. Illustrative of such references are the following:

1. J.Am.Chem.Soc.,81,197–201(1959) discloses the synthesis of compounds having the formula:



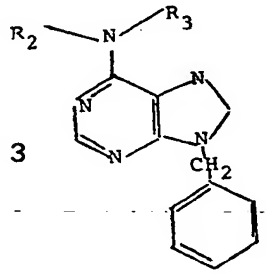
wherein R is cyclohexyl or 2-cyclohexenyl. The compounds were prepared as potential anticancer agents.

2. U.S. Patent 3,917,837 discloses the use of the compound:



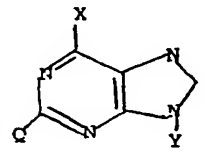
as an anti-inflammatory agent.

3. U.S. Patent 3,930,005 discloses compounds of the formula:



wherein R_2 and R_3 may be *inter alia* hydrogen and R_1 may be *inter alia* (lower) alkoxy. The compounds are said to possess anti-inflammatory activity.

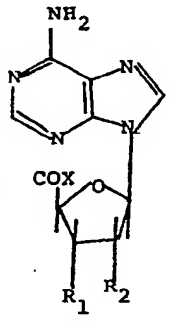
4. Belgian Patent 853,086 (Farmdoc 70719Y) discloses compounds of the formula:



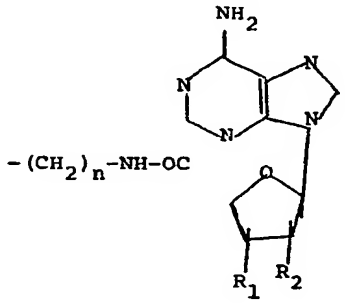
wherein *either* X is C_1-C_6 alkoxy or -NAAR; R is H or (lower)alkyl; Y is C_1-C_6 alkyl, C_1-C_{10} cycloalkyl or hydroxycycloalkyl, phenyl, halophenyl, trifluoromethyl-phenyl, bicycloalkyl or hydroxy-bicycloalkyl of up to 12 carbons, or -AR′; A is methyl ne or ethylene; R¹ os phenyl, halophenyl, trifluoromethyl-phenyl, bicycloalkyl or hydroxy-bicycloalkyl of up to 12 carbons; Q is

H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl or hydroxycycloalkyl, bicycloalkyl or hydroxybicycloalkyl of up to 12 carbons, phenyl, halophenyl, trifluorom thyl-phenyl or AR^1; *or* X is halogen or (lower)-dialkylamino; Y is methyl, ethyl, cyclop ntyl, phenyl, halophenyl, trifluoromethyl-ph nyl or benzyl and Q is an previously defined. The compounds are reported to be useful in treating psoriasis.

5. West German Published Application 2,610,985 (Farmdoc 70863Y) discloses compounds of the formula:

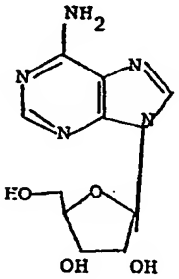


wherein R_1 and R_2 are OH or ONO_2, or togehter form C_2-C_7 alkylidene, aralkylidene or CR_4R_5;R_4 is H or C_1-C_7 alkyl; R_5 is OR_6 or NR_7R_8; R_6 is C_1-C_7 alkyl; R_7 and R_8 are optionally substituted C_1-C_7 alkyl or C_3-C_7 cycloalkyl, or together form a C_2-C_5 alkylene group in which one CH_2 group is optionally replaced by a heteroatom; R_3 is C_1-C_7 alkyl or alkoxy, optionally substituted phenyl or H; X is OR_9 or $NR_{10}R_{11}$; R_9 is C_1-C_7 alkyl, C_3-C_7 cycloalkyl, optionally substituted phenyl or aralkyl; R_{10} and R_{11} are H, optionally substituted C_1-C_7 alkyl, alkenyl or alkynyl, optionally substituted C_3-C_7 cycloalkyl, substituted phenyl, benzylamino, 2-methylfuryl or adamantyl, or one can be H and the other a group of the formula:



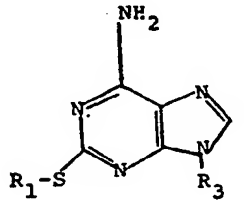
wherein n is 2–16, or R_{10} and R_{11} together form a C_2-C_5 alkylene group in which one CH_2 group can be replaced by a heteroatom. The compounds are said to have circulatory, cardiac and metabolic activity.

6. *Chem.Pharm.Bull.,23*(4), 759–774(1975) discloses *inter alia* compounds of the formula

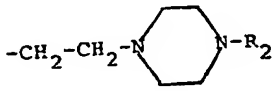


wherein R is (lower)alkyl. The compounds are said to have coronary vasodilating activity.

7. Japanese Published Application 52–71492 (Farmdoc 53190Y) discloses compounds of the formula

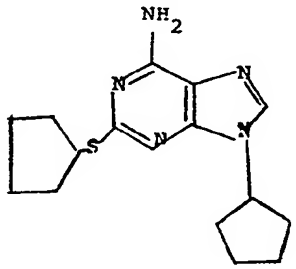


wherein R_1 is C_1-C_{10} straight or branched alkyl, C_5-C_{10} cycloalkyl, C_7-C_{11} aralkyl or piperazinoethyl of the formula:



wherein R_2 is C_7-C_{11} aralkyl, mono-substituted aralkyl, cinnamyl or fluorenyl; R_3 is C_1-C_{10} straight or branched alkyl, C_5-C_{10} cycloalkyl, C_7-C_{11} aralkyl or piperazinoethyl as defined above, with the exclusion of compounds in which R_1 and R_3 are methyl, R_1 is methyl and R_3 is ethyl and R_1 is C_5-C_{10} cycloalkyl and R_3 is C_1-C_4 alkyl, C_5-C_{10} cycloalkyl or C_7-C_{11} aralkyl. The compounds are reported to show an inhibitory effect on blood platelet aggregation and to have coronary dilating activity.

8. Chem Pharm. Bull., *25*(7), 1811–1821 (1977) discloses preparation of 2-thioadenosine derivatives including *inter alia* a compound of the formula:

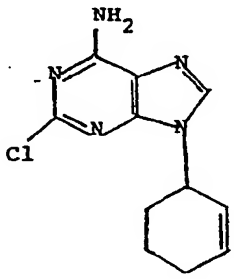


The above compound is reported to be slightly effective as a platelet aggregation inhibitor. The authors note that the corresponding compound having a ribose sugar moiety at the 9-position was far more effective and conclude that the ribosyl moiety of 2-thioadenosine derivatives is essential for effective inhibition of platelet aggregation and cannot be replaced by other substituents.

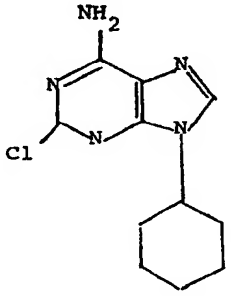
No reference have been found disclosing 2,9-disubstituted adenine derivatives having a chloro substitutent at the 2-position and a cycloalkyl or cycloalkenyl group at the 9-position.

The present invention is concerned with novel purine intermediates that can be converted into derivatives which effectively inhibit bronchial constriction induced by histamine or other bronchial constricting substances. The purine derivatives belong to the non-adrenergic class of bronchodilators and are useful for administration to mammals in the treatment of asthma including bronchial asthma, allergic asthma, bronchitis, pulmonary emphysema and other chronic respiratory diseases involving bronchospasm. The compounds of the invention also have been shown by standard pharmacological test procedures to have superior bronchodilator activity relative to aminophylline with reduced cardiovascular and central nervous system side effects.

The compounds of the present invention have the structures:



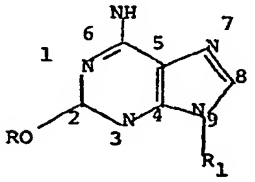
and



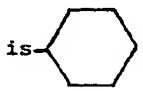
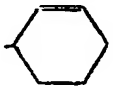
II II'

which can be readily converted by processes described hereinafter into the compounds of formula I.

The purine derivatives have the structure



I

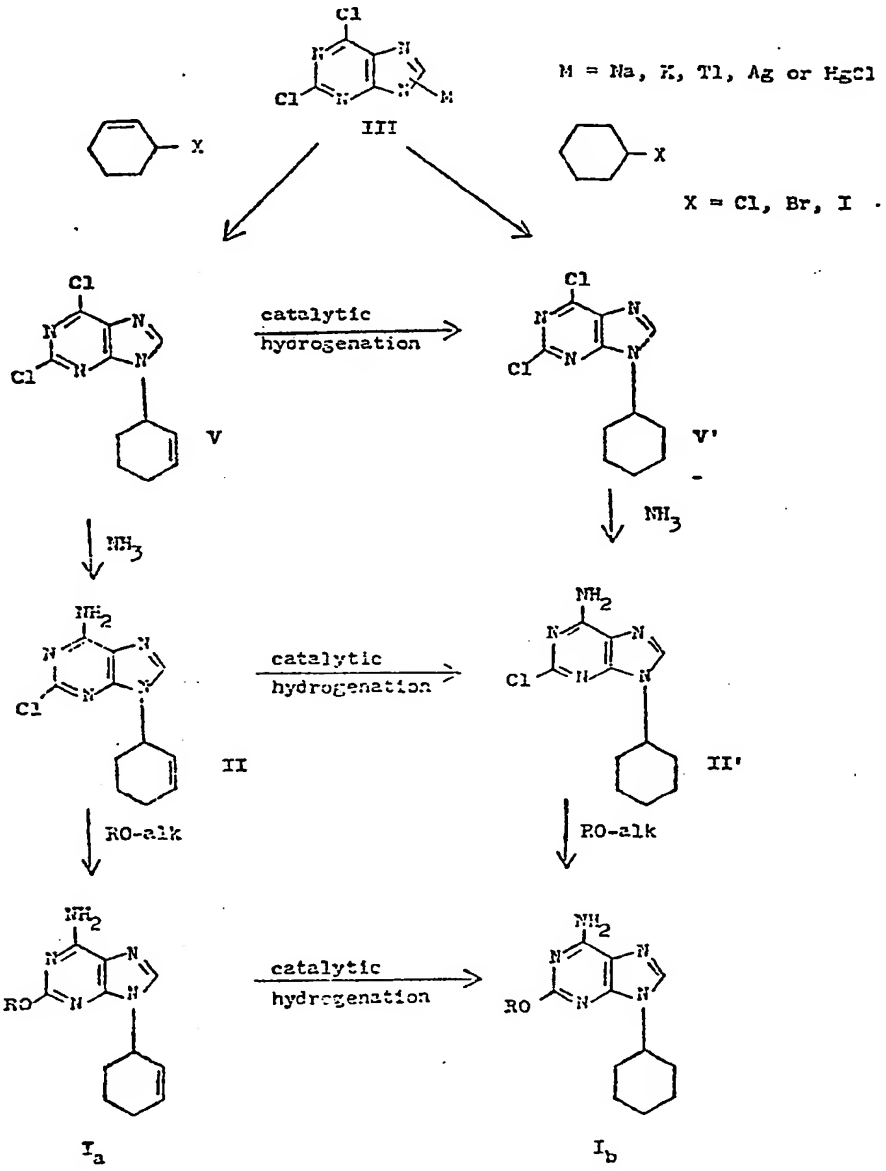
and pharmaceutically acceptable acid addition salts thereof, wherein R is C_1-C_6 alkyl and R_1 is  or 

and these are further described in Patent Application No. 79.15401 from the present application is a divisional application.

The term "pharmaceutically acceptable acid addition salts" as used herein includes those salts formed from mineral acids such as hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, and the like; and also organic acids such as acetic, citric, pivalic, lactic, tartaric, oxalic, succinic, maleic and the like. Any non-toxic acid which forms a salt with the present compounds is suitable. The salts are prepared by conventional methods well known to the art.

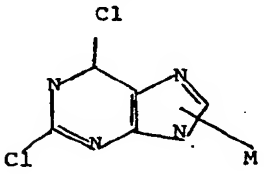
The C_1-C_6 alkyl groups referred to above include those having either straight or branched hydrocarbon chains. Particularly preferred alkyl groups are those having from 1 to 4 carbon atoms. Examples of suitable C_1-C_6 alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl, n-pentyl, n-hexyl, and the like.

The compounds of formula II or II' may be prepared by the general reaction scheme depicted below.


M = Na, K, Tl, Ag or HgCl
X = Cl, Br, I
III
catalytic hydrogenation
V
V'
NH3
catalytic hydrogenation
II
II'
RO-alk
catalytic hydrogenation
Ia
Ib

Compounds of formula II may be prepar d from 2,6-dichlor purin , a known compound, by the proc ss comprising the consecutive steps of

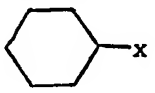
1) reacting 2,6-dichloropurine with about one equivalent of $HgCl_2$ or a source of Na^+, R^+, Tl^+ or Ag^+ (i.e. a salt which dissociates to form the desired ion) in an inert solvent to produce a metal derivative having the formula:



III

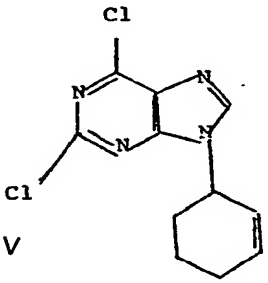
wherein M is HgCl, Na, K, Tl or Ag;

2) condensing metal derivative III in a substantially anhydrous inert organic solvent with a 3-halocyclo-hexene of the formula



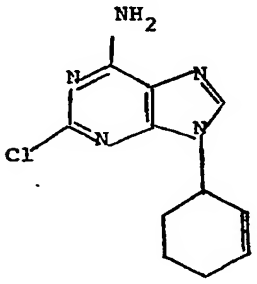
Iv'

wherein X is chloro, bromo or iodo to produce a compound having the formula:



V

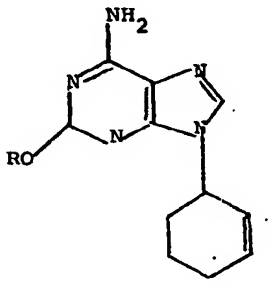
3) subjecting compound V to amination with NH_3 in an inert solvent to produce a compound having the formula:



II

The intermediate II may be further converted into the compound of formula (I) wherein R_1 is R is 2-cyclo hexenyl by heating compound II with an alkali metal-alkoxide of the formula RO-alk wherein alky represents sodium or potassium and R is as defined above in an inert solvent to produce the desired free base produce of formula I and, if desired, converting said product by methods known *per se* to a pharmaceutically acceptable acid addition salt thereof.

A preferred method of preparing a compound of the formula:



I_a

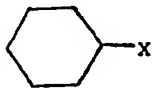
wherein R is C_1-C_6 alkyl, or a pharmaceutically acceptable acid addition salt thereof comprises heating intermediate II with an alkali metal alkoxide of the formula RO-alk wherein alk represents sodium or potassium and R is as defined above in an inert solvent until the desired free base product is formed and, if desired, coverted said product by methods known *per se* to a pharmaceutically acceptable acid addition salt thereof.

Compounds of formula II′ may be prepared by catalytic hydrogenation of the compound of formula II. As an example of a suitable procedure, a compound of formula II′ may be dissolved in a suitable non-reducible, inert solvent (e.g. methanol, ethanol, water aqueous methanol, aqueous ethanol) and then hydrogenated using a conventional hydrogenation catalyst. Examples of suitable catalysts include palladium black, Pd-$BaSO_4$, Pd-C, PtO_2, Rh-C, Raney nickel, CuCrO, RhCl $[P(C_6H_5)_3]_3$ and RuCl $[P(C_6H_5)_3]_3$. A preferred catalyst is palladium-on-carbon. While temperature and pressure are not critical for the hydrogenation step, advantageous results have been achieved under conditions of room temperature and atmospheric pressure.

A process for preparing compounds of formula II′ comprises the consecutive steps of

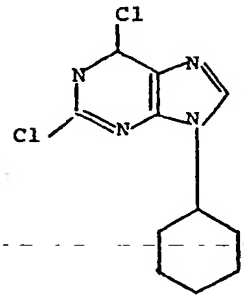
1) reacting 2,6-dichloropurine with about one equivalent of $HgCl_2$ or a source of Na^+, K^+, Tl^+ or Ag^+ in an inert solvent to produce metal derivative III;

2) condensing metal derivative III in a substantially anhydrous inert organic solvent with a cyclohexyl halide of the formula



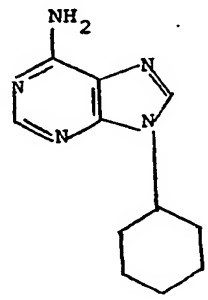
Iv′

wherein X is chloro, bromo or iodo to produce a compound having the formula:



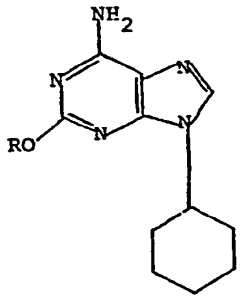
V′

3) subjecting compound V′ to amination with NH_3 in an inert solvent to produce a compound having the formula



II′

Th intermediate II′ may be used to prepare the desired free base of formula I by heating intermediat II with an alkali metal alkoxide of the formula RO-alk wherein alk represents sodium or potassium and R is as defined above in an inert solvent to produce the desired free base product of formula I and, if desired, converting said product by methods known *per se* to a pharmaceutically acceptable acid addition salt thereof. Intermediate II may also be used to prepare a compound of the formula



I_b

wherein R is C_1-C_6 alkyl, or a pharmaceutically acceptable acid addition salt thereof. Intermediate II′ is heated with an alkali metal alkoxide of the formula RO-alk wherein alk represents sodium or potassium and R is as defined above in an inert solvent until the desired free base product is formed and, if desired, converting said product by methods known *per se* to a pharmaceutically acceptable acid addition salt thereof.

Preparation of the 2,6-dichloropurine metal derivatives of formula III may be accomplished by methods previously described in the literature and in our co-pending patent application No. 79.15401.

The chloromercuri salt is the preferred metal derivative for use in the processes of the present invention.

Metal derivative III is condensed with a 3-halocyclohexane, preferably 3-bromocyclohexane, or a cyclohexyl halide to produce respectively, intermediate V or V′. Reaction conditions may be substantially the same as those employed in the conventional nucleoside synthesis [see, e.g. *J. Am.Chem.Soc.,81,*197–201(1959)]. In a preferred embodiment the 3-halocyclohexane or cyclohexyl halide is added, preferably in excess, to compound III in an inert substantially anhydrous organic solvent such as an aromatic hydrocarbon (e.g. benzene, xylene, toluene) and the reaction mixture is heated under reflux to form intermediate V or V′.

Amination of the so-produced intermediate to replace the 6-chloro substituent with a 6-amino group may be carried out by conventional procedures [see, e.g. *Chem.Pharm.Bull.,23,* 759–774 (1975)]. In a preferred embodiment intermediate V or V′ is suspended in an inert solvent (e.g. water, methanol, ethanol), the suspension is saturated with ammonia gas (preferably at a reduced temperature such as −0°C) and the saturated reaction mixture is then heated at a temperature of from just above room temperature to the boiling point of the reaction medium. A most preferred amination procedure comprises heating a solution of the appropriate intermediate in methanolic ammonia in a sealed tube at about 100°C. Compounds II and II′ are potent bronchodilator agents as well as intermediates in the preparation of the 2-alkoxy products of formula I.

Intermediate II or II′ may then be subjected to a nucleophilic substitution reaction to convert the 2-chloro substituent to a 2-alkoxy group. This step may be carried out by the general procedure disclosed in West German Published Application 2,258,378. In a preferred embodiment intermediate II or II′ is heated with a solution of an alkali metal (lower)alkoxide (RONa or ROK where R is C_1-C_6 alkyl) in an inert solvent (e.g. benzene, dimethylformamide or a C_1-C_6 alkanol). If a (lower)alkanol solvent is used, both the alkanol and alkoxide used in this step should contain the same "R" substituent. While the temperature for the reaction is not critical, it is preferred to carry out the substitution at reflux temperature so as to maximize the yield and minimize the reaction time. At the conclusion of the reaction, any excess base in the reaction mixture is neutralized with acid and the desired free base product recovered as by evaporation to dryness.

Fr e base products of formula I, II or II′ may be conv rted to pharmaceutically acceptable acid addition salts by conventional methods. Thus, for example, th free base may be dissolv d in an inert solvent, reacted with about one equivalent weight of a suitabl organic or inorganic acid to produce th desired salt, and the salt recovered as by solv nt precipitation or lyophilization.

The pharmacologically active compounds of the present inv ntion may b administer d ither as individual therap utic agents or as mixtures with other therap utic agents. They may be administered alone, but are g n rally given in th form of pharmaceutical compositions. Examples of such compositions include tablets, lozenges, capsules, powders, aerosol sprays,

aqueous or oily suspensions, syrups, elixirs and aqueous solutions. The compounds are preferably administered orally, but may also be given by inhalation or injection.

The nature of th pharmaceutical composition and the pharmac utical carrier or diluent will, of course, depend on the desired route of administration. For example, oral compositions may be in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g. syrup, acacia, gelatin, sorbitol, tragacanth or polyvinylpyrrolidone), fillers (e.g. lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine), lubricants (e.g. magnesium stearate, talc, polyethylene glycol or silica), disintegrants (e.g. starch) or wetting agents (e.g. sodium lauryl sulfate). Oral liquid preparations may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups, elixirs, etc. or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, flavoring agents, diluents or emulsifying agents.

Pharmacological Tests

The compound of Formula II of the present invention was examined comparatively with aminophylline to determine *in vitro* and *in vivo* brochodilator activity and *in vivo* hypotensive activity (a measure of cardiovascular side effect).

In Vitro Bronchodilator Activity

Trechael chains of guinea pig were prepared by the method described by A. Akcasu in *Arch. Int.Pharmacodyn Ther., 122,* 201 (1959). The response to each compound was recorded by the Magnus method and expressed as a percentage of the maximum response obtained with 0.1 mcg/ml. of isoproterenol prior to each experiment. Bronchodilator activity (in vitro) of aminophylline and the test compound is expressed in Table 1 below as an EC_{50} value (concentration in mcg/ml. which produces a relaxation which is 50% of the maximum response to 0.1 mcg/ml of isoproterenol).

In Vivo Bronchodilator and Hypotensive Activity

The *in vivo* bronchodilator activity of aminophylline and the test compound was evaluated by an increase in the intratracheal pressure (ITP) of guinea pig by a modification of the method described by James in *J.Pham.Pharmac., 21,*379 (1969). The trachea of anesthetized guinea pig was cannulated and the ITP recorded on a polygraph under artificial ventilation. Arterial blood pressure (ABP; measure of hypotensive activity) was also measured during the experiment. Data was obtained for both intravenous and intraduodenal administration. Table 1 expresses the *in vivo* bronchodilator activity (ITP) of each compound as an ED_{50} value (dose in mg/kg. resulting in a 50% decrease in intratracheal pressure) and the hypotensive activity (ABP) as an ED_{20} value (dose in mg/kg which reduces arterial blood pressure by 20%).

Separation of Bronchodilator and Cardiovascular Effects

To assess the separation of desirable bronchodilator activity from undesirable cardiovascular (hypotensive) effect in the test compounds, the ratio of hypotensive ED_{50}/bronchodilating ED_{50} was calculated and indicated in Table 1. The compound exhibiting the largest ABP/ITP ratios has the greatest separation of cardiovascular side effect from bronchodilator activity.

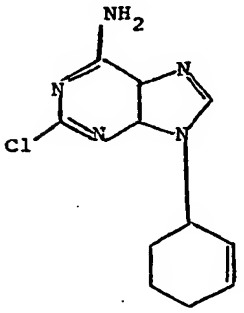
Table 1
Pharmacological Test Results

	In vitro	*In vivo*					
		Intravenous			Intraduodenal		
	ITC, EC_{50} (mcg./ml.)	ITP, ED_{50} (mg./kg.)	ABP, ED_{50} (mg./kg.)	ABP/ITP	ITP, ED_{50} (mg./kg.)	ABP, ED_{50} (mg./kg.)	ABP/ITP
Compound II	0.12	0.15	2.5	17	—	—	—
aminophylline	16.6	0.58	1.18	2	5.9	9.5	16

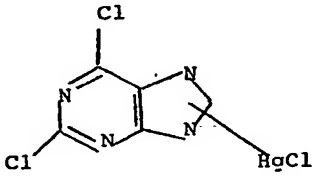
ITC = activity in the isolated tracheal chain ABP = arterial blood pressure lowering activity
ITP = activity in the intratrachael pressure test

The following examples are intended to be illustrative of the present invention.

Example 1
2-Chloro-9-(2-cyclohexenyl)-9H-adenine

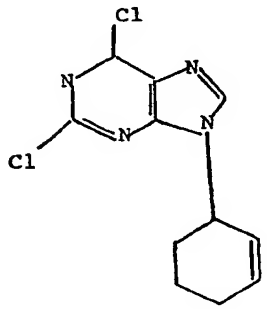


A. *HgCl Salt of 2,6-dichloropurine*



To a stirred solution of 7.38 g (27.2 mmoles) of $HgCl_2$ in 100 ml. of 50% ethanol was added 5.51 g. (27.2 mmoles) of 2,6-dichloropurine. After 5 minutes, 10% NaOH ~W10 ml). was added to the solution until no more color reaction (yellow due to HgO) occurred. The mixture was stirred for 30 minutes and the precipitate was filtered, washed successively with water, ethanol and diethyl ether, and dried to give 6.91 g (64% yield) of the title salt.

B. *9-(2-Cyclohexenyl)-9H-2,6-dichloropurine*



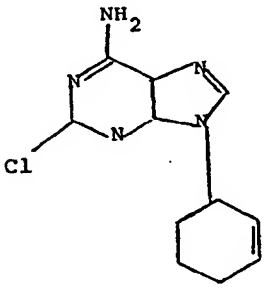
A mixture of 6.91 g (16.3 mmoles) of the product of step A and 6.91 g. of "Celite" (diatomaceous earth) in benzene was azeotropically evaporated to remove moisture. To the resulting mixture was added 100 ml. of dry xylene and 4 ml. (339 mmoles) of 3-bromocyclohexene. The mixture was refluxed for 2.5 hours with agitation, cooled and filtered. The filter cake was washed with a small amount of $CHCl_3$. The filtrate and wash were evaporated to dryness. The residue was dissolved in 50 ml. of benzene and the solution washed with 20% KI solution (3 times) and aqueous NaCl (once) and dried with Na_2SO_4. The filtrate was evaporated and the residue purified by chromatography on silica gel to give 3.87 g (88%) of the title compound; m.p. 133–135°C IR(KBr): 2930, 1590, 1565, 1405, 1355, 1315, 1210, 875, 835 cm^{-1}.

UV: λ_{max}^{MeOH} 267 nm (ξ9500).

NMR ($CDCl_3$): δ2.00(6H, m), 5.60(1H,m), 6.00(2H,m), 8.11(1H,s).
Anal. Calcd for $C_{11}H_{10}N_4Cl_2$: C,49.09; H,3.75; N, 20.82 Cl,26.35.

Found: C,48.54; H 3.48; N, 20.34;
Cl, 25.54

C. *2-Chloro-9-(2-cyclohexenyl)-9H-adenine*

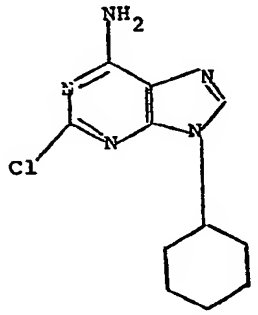


Ammonia gas was bubbled into a mixture of 2.8 g (10.3 mmoles) of 9-(2-cyclohexenyl)-9H-2,6-dichloropurine in 50 ml. of CH_3OH at 0°C. until no more gas was absorbed. The mixture was heated at 100°C for 4 hours in a sealed tube, then cooled and concentrated to deposit crystals, which were filtered to afford 2.39 g. of the title compound. A second crop (112 mg) was obtained from the filtrate by chromatographical separation over silica gel. Total yield = 2.50 g (96%); m.p. 195–197°C IR(KBr): 3120,1640,1590,1320,1300,1225,1190,920 cm^{-1}.

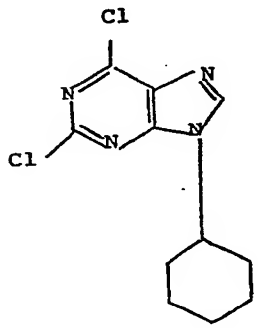
UV λ_{max}^{MeOH} 266nm

(ξ14600). NMR ($CDCl_3$): δ0.89(1H,m), 1.26 (1H,m),2.00 (4H,m), 5.30(1H,m),6.00(2H, m),8.11(1H,s).

Example 2
2-Chloro-9-cyclohexyl-9H-adenine

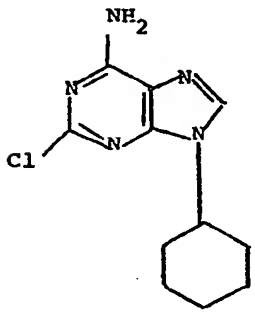


A. *9-Cyclohexyl-9H-2,6-dichloropurine*



If in the procedure of Example 1B the 3-bromocyclohexane used therein is replaced by an equivalent weight of cyclohexyl bromide, the titl compound is produced.

B. *2-Chloro-9-cyclohexyl-9-adenine*



If the procedure of Example 1C is repeated with the 9-(2-cyclohexenyl)-9H-2,6-dichloropurine used therein replaced by an equivalent weight of 9-cyclohexyl-9H-2,6-dichloropurine, there is produced the title compound.

Example 3
2-Chloro-9-cyclohexyl-9H-adenine

A mixture of 2-chloro-9-(2-cyclohexenyl)-9H-adenine[1] (252 mg.; 1.0 mmol) in ethanol was hydrogenated with 10% palladium-on-charcoal (93 mg) at room temperature and under atmospheric pressure. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by silica gel chromatography to give 139 mg (55%) of the title compound; m.p. 206–209°C.

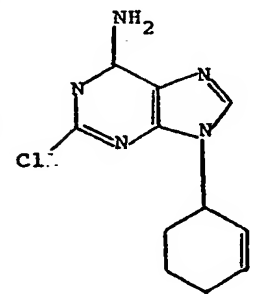
IR (Kbr): 3360,3150,2905,1645,1595,1570, 1540 cm^{-1}.

UV: $\lambda_{max}^{C_2H_5OH}$ 267 nm (ξ15,300).

NMR ($CDCl_3$): δ1.80 (10H,m),4.47 (1H,m),6.23 (2H,s),7.82 (1H,s).

CLAIMS

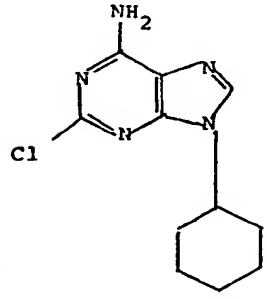
1. A compound of the formula:



II

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of the formula:



II'

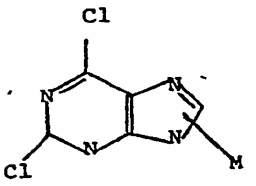
or a pharmaceutically acceptable acid addition salt thereof.

3. A process for the preparation of a compound as claimed in claim 1 which process

1. Prepared from 2,6-dichloropurine according to the procedure of Example 1.

c nstitute the steps:

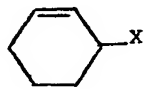
1) r acting 2,6-dichloropurine with about one equivalent of $HgCl_2$ or a source of Na^+, K^+, Tl^+ or Ag^+ (i.e. a salt which dissociates to form the d sired ion) in an inert solvent to produc a metal derivative having the formula :



III

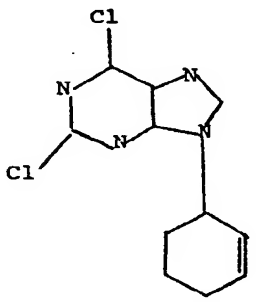
wherein M is HgCl, Na,K,Tl or Ag;

2) condensing metal derivative III in a substantially anhydrous inert organic solvent with a 3-halocyclohexene of the formula:



IV

wherein X is chloro, bromo or iodo to produce a compound having the formula:



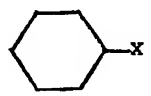
V

3) subjecting compound V to amination with NH_3 in an inert solvent to produce a compound of formula (ii) as given in claim 1.

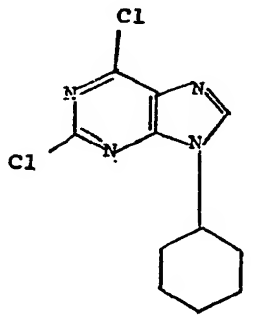
4. A process for the preparation of a compound as claimed in claim 2 which comprises the consecutive steps of

1) reacting 2,6-dichloropurine with about one equivalent of $HgCl_2$ or a source of Na^+, K^+, Tl^+ or Ag^+ in an inert solvent to produce metal derivative III;

2) condensing metal derivative III in a substantially anhydrous inert organic solvent with a cyclohexyl halide of the formula:



wherein X is chloro, bromo or iodo to produce a compound having the formula:



V'

3) subjecting compound V' to amination with NH_3 in an inert solvent to produce a compound

of formula II' as given in claim II.

5. A process as claimed in claim 3 substantially as hereinbefore described with reference to Exampl 1.

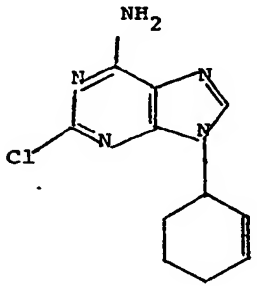
6. A compound as claimed in claim 1 whenever produced by a process as claimed in claim 3 or claim 5.

7. A process as claimed in claim 4 substantially as hereinbefore described with reference to Example 2 or Example 3.

8. A compound as claimed in claim 2 whenever prepared by a process as claimed in claim 5 or claim 7.

CLAIMS (4 Jun 1982)

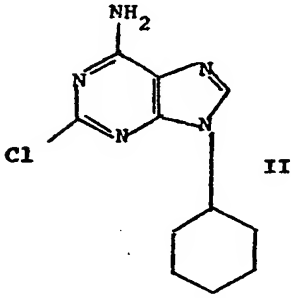
1. A compound of the formula:



II

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of the formula:

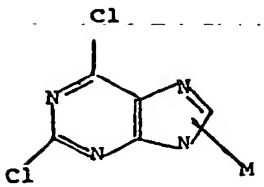


II

or a pharmaceutically acceptable acid addition salt thereof.

3. A process for the preparation of a compound as claimed in claim 1 which process constitute the steps:

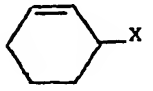
1) reacting 2,6-dichloropurine with about one equivalent of $HgCl_2$ or a source of Na^+, K^+, Tl^+ or Ag^+ (i.e. a salt which dissociates to form the desired ion) in an inert solvent to produce a metal derivative having the formula:



III

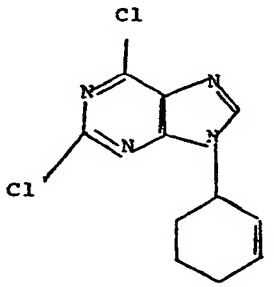
wherein M is HgCl, Na,K,Tl or Ag;

2) condensing metal derivative III in a substantially anhydrous inert organic solvent with a 3-halocycloh xen of the formula:



IV

wherein X is chloro, bromo or iodo to produce a compound having the formula:



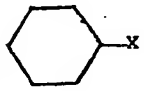
V

3) subjecting compound V to amination with NH_3 in an inert solvent to produce a compound of formula (ii) as given in claim 1.

4. A process for the preparation of a compound as claimed in claim 2 which comprises the consecutive steps of

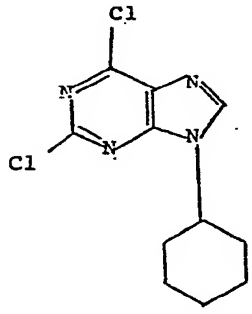
1) reacting 2,6-dichloropurine with about one equivalent of $HgCl_2$ or a source of Na^+, K^+, Tl^+ or Ag^+ in an inert solvent to produce metal derivative III;

2) condensing metal derivative III in a substantially anhydrous inert organic solvent with a cyclohexyl halide of the formula:



IV'

wherein X is chloro, bromo or iodo to produce a compound having the formula:



V'

3) subjecting compound V' to amination with NH_3 in an inert solvent to produce a compound of formula II' as given in claim 2.

5. A process as claimed in claim 3 substantially as hereinbefore described with reference to Example 1.

6. A compound as claimed in claim 1 whenever produced by a process as claimed in claim 3 or claim 5.

7. A process as claimed in claim 4 substantially as hereinbefore described with reference to Example 2 or Example 3.

8. A compound as claimed in claim 2 whenever prepared by a process as claimed in claim 5 or claim 7.

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